June 10, 2019

Mr. Stiven Foster
Science Advisor
Office of Land and Emergency Management
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Re: Draft Interim Recommendations for Addressing Groundwater Contaminated with Perfluorooctanoic Acid and Perfluorooctane Sulfonate; Docket No. EPA-HQ-OLEM-2019-0229

Dear Mr. Foster:

The American Chemistry Council[1] appreciates the opportunity to comment on the draft Interim Recommendations for Addressing Groundwater Contaminated with Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS). ACC is deeply concerned about the scientific basis for the draft recommendations, as well as the process that led to their issuance.

The draft guidance proposes the following recommendations –

- a preliminary remediation goal (PRG) of 70 parts per trillion (ppt) for PFOA and PFOS in groundwater used or potentially used as drinking water, based on EPA's 2016 lifetime health advisories (LHAs), and
- a groundwater screening level of 40 ppt for these two substances based on a Hazard Quotient (HQ) of 0.1.

The LHAs have not been subject to sufficiently robust peer review to support their use as PRGs. The Agency proposal to set the screening level based on an HQ of 0.1, moreover, is not supported by the available science and is not consistent with Agency policy. For the reasons outlined below, we encourage EPA to ensure that cleanup levels for PFOA and PFOS – whether issued as recommendations or as enforceable limits – be based on the weight of the best

[1] ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing.

available scientific evidence, be consistent with current EPA guidance, and be subject to robust review.

Preliminary Remediation Goals

In releasing the LHAs for PFOA and PFOS in 2016, EPA cautioned that health advisories "are non-enforceable and non-regulatory" and are intended to "provide technical information to states agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination." As such, it is inappropriate to use these values as remediation goals where no applicable or relevant and appropriate requirements (ARARs) exist – particularly in light of the concerns identified below.

EPA's Office of Water released draft health effects documents supporting the development of LHAs for PFOA and PFOS in February 2014.[2] A scientific peer review meeting was subsequently held in August 2014 during which the reviewers raised a number of questions and concerns about the draft documents.[3] Among the concerns expressed were the selection of the health end point used as a basis for deriving the reference dose (RfD) and the use of an older physiologically based pharmacokinetic (PBPK) model for predicting human serum levels.

As a result of the comments received, the Office of Water revised its selection of the key health endpoints but did not recirculate the revised analysis for appropriate peer review before finalizing the LHAs. In finalizing the advisories, the Water Office also added a recommendation that "the health advisory guideline be applied as the sum of the concentrations" of PFOA and PFOS – a recommendation that was not subject to public comment or peer review.

In finalizing the Health Advisories, moreover, the Office of Water did not agree with the recommendation to use more recent models to predict human serum levels, despite a reviewer's caution that –

> The choice of using the empirical model over the more recent physiological models may be a weakness [as] our understanding of transporters advance. The evolution of chemical-specific PBPK models for use in risk assessment and regulatory applications has repeated itself several times. [That] is, the first empirical non-physiological model(s) or PBPK models contain hypotheses generating ideas and later models test some of these hypotheses, especially if

---

2 http://www.gpo.gov/fdsys/pkg/FR-2014-02-28/pdf/2014-04455.pdf

3 Versar. Peer review summary report – external peer review of EPA's draft health effects documents for perfluorooctanoic acid and perfluorooctane sulfonate (PFOS). Prepared for EPA Office of Water, Office of Science and Technology (November 17, 2014). https://www.regulations.gov/document?D=EPA-HQ-OW-2014-0138-0027

> additional experimental data become available. In the case of PFOA and PFOS, the EPA selected not to use the most recent PBPK models for PFOA and PFOS, but instead use a computational empirical based model . . . that was the first attempt to quantitatively interpret the kinetics of PFOA and PFOS across species of laboratory animals.[4]

In its response, the Office of Water noted that "a [PBPK] model for PFAS would be preferable because it would allow extrapolation between species, provide better estimates of chemical-specific parameters, and allow estimation of chemical concentration in the specific tissues for which toxicity is observed."[5] The response reasoned, however, "that the state of the science has not yet developed such that extrapolation between species is possible." This is no longer the case.

Since the LHAs were finalized, two significant scientific work products have become available that advance our understanding of the pharmacokinetics of PFOA and PFOS and allow for a more effective extrapolation between species. The first of these is the recently completed assessments of maximum allowable concentrations for PFOA and PFOS in drinking water from Health Canada that incorporate the newer PBPK models recommended by the peer reviewer.[6] The second new source of information is the availability of data from a human clinical trial conducted to explore the potential therapeutic action of ammonium perfluorooctanoate.[7] The clinical data includes dose-response, time-course measurements of PFOA that allow better scientific estimates of the half-life of PFOA in humans. From the standpoint of using knowledge of the kinetics in humans as the foundation for developing LHAs, these recent studies are the best available science.

Large pharmacokinetic differences exist between humans and animals for PFOA and PFOS, with lower clearance (i.e., higher half-life values) reported for humans than for rats, mice, and non-human primates. These differences can result in higher target tissue doses in humans when exposed to the same external doses as laboratory animals. To better account for these interspecies toxicokinetic differences in developing the LHAs, the Office of Water calculated a

---

4 Ibid, at 39.

5 EPA. EPA response to external peer review comments on EPA draft documents; health effects support document for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Office of Water, Office of Science and Technology (May 2016). https://www.regulations.gov/document?D=EPA-HQ-OW-2014-0138-0036

6 https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality.html

7 This work is summarized in Convertino M *et al.* Stochastic pharmacokinetic-pharmacodynamic modeling for assessing the systemic health risk of perfluorooctanoate (PFOA). *Toxicol Sci* 163(1):293–306 (2018). https://doi.org/10.1093/toxsci/kfy035

human equivalent dose (HED) by adjusting the serum concentration in rodents exposed via the drinking water route by the rate of estimated clearance (CL) of the substance from the human body. The CL was calculated using the estimated volume of distribution and serum elimination half-life estimated from empirical data.[8]

Compared to the approach that relied on older scientific data, the internal-dose ratios predicted by the more recent PBPK models indicate that the interspecies extrapolations for PFOA and PFOS are highly dose dependent and result from nonlinear toxicokinetics.[9] Evidence that the half-life in humans is dose-dependent indicates that a single interspecies extrapolation factor such as that used by EPA's Office of Water is not scientifically supportable for either PFOA or PFOS. Instead, using the new PBPK model to derive data for environmentally relevant exposure levels is a more scientifically appropriate approach for addressing the issue of nonlinear toxicokinetics and its impact on interspecies extrapolation.

Accordingly Health Canada compared dose metrics predicted by the various animal PBPK models to calculate a CL ratio between species (CL_{animal}/CL_{human}).[10] Using the model data to derive the CL ratio allows for a more appropriate comparison of exposures and doses of the same magnitude.[11] Based on this approach, Health Canada's analysis indicates that the EPA significantly underestimates the human clearance rate in deriving the LHAs.[12] As a result, the HEDs that EPA derived to calculate the 2016 LHAs are up to 500 times lower than what the new, best available science indicate.[13]

---

[8] The volume of distribution is defined as the volume of blood (in milliliters per kilogram) in which the amount of a chemical would need to be uniformly distributed to produce the observed blood concentration. Half-life is a measure of the time (in days) required to eliminate one half of a quantity of a chemical from the body.

[9] Loccisano AE *et al.* Comparison and evaluation of pharmacokinetics of PFOA and PFOS in the adult rat using a physiologically based pharmacokinetic model. *Reprod Toxicol* 33(4):452–467 (2012). https://doi.org/10.1016/j.reprotox.2011.04.006

[10] For each species, the PBPK model was used to predict internal doses for a broad range of oral doses. Model simulations were continued until steady-state conditions or expected lifetimes were reached (Loccisano *et al.* 2012).

[11] Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document - Perfluorooctane Sulfonate. Ottawa, Ontario (2018), at 36.

[12] Based on the clearance ratio calculation, Health Canada adjusted the animal doses by factors of 0.0104 and 0.071 for PFOA and PFOS, respectively, compared to EPA's adjustment factor of 0.00014 for PFOA and 0.000081 for PFOS.

[13] Other assumptions may have changed since the 2016 LHAs were developed. For example, the water consumption rate for lactating women, on which the LHAs were based, was reduced from 55 to 47 milliliters per kilogram per day in the February 2019 update of Chapter 3 of EPA's Exposure Factors Handbook. https://www.epa.gov/expobox/about-exposure-factors-handbook

The conclusions reached by Health Canada also are supported by recent observations from a clinical study that explored the potential therapeutic action of PFOA (see Figure 1). These studies indicate that PFOA levels in humans may reach steady state after only about 25 weeks of exposure and suggest that half-lives in humans may be as short as 5 weeks[14] – in contrast to the 2.3 years assumed by EPA for the 2016 LHA.[15] While these newer human clinical data should be interpreted with caution, since the kinetics from these studies may not reflect the average population, these scientific investigations represent one of the few longitudinal studies of plasma levels in humans currently available.

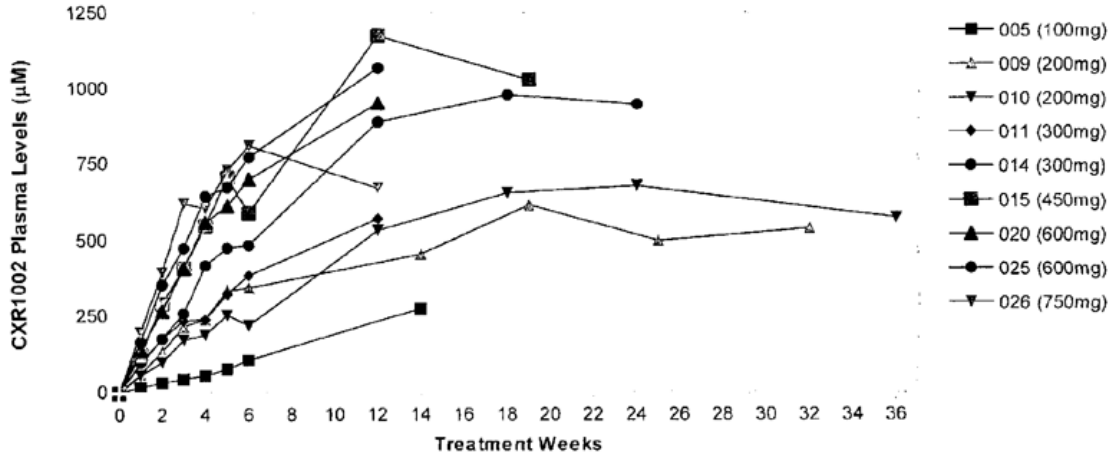

Figure 1. Plasma levels of PFOA after administration of ammonium perfluorooctanoate.[16]

Screening Levels

The description of EPA's derivation of the draft screening level is brief, but indicates that the Agency used the RfDs generated by the Office of Water and an HQ of 0.1. In explaining the rationale for not using the default HQ of 1.0 per Superfund guidance, the draft points to the specific and limited purpose of a screening level, the additive toxicity of PFOA and PFOS, and the possible co-location of other PFAS compounds for which toxicity values may not currently be available.

[14] Shinya I. Pharmacokinetics 101. *Paediatr Child Health* 16(9): 535-536 (2011). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3223885/

[15] https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final_508.pdf

[16] Elcombe CR *et al.* Compositions comprising perfluoroctanoic acid. US Patent application publication no. US 2013/0029928 Al (January 31, 2013). Enclosed.

As explained in the previous section, the RfDs calculated as part of the derivation of the LHAs for PFOA and PFOS do not reflect the best and most current science and should be evaluated in light of the information that has become available since they were developed. While Superfund guidance does suggest that an HQ of 0.1 may be used as an initial screening target, the guidance explains that such an approach should be applied "where more than one chemical with the same toxic endpoint might be present."[17] Such an assumption clearly cannot be made for the other PFAS for which toxicity values are not available. It should be vigorously evaluated in light of a substantial body of evidence to support differences across PFAS in terms of physical-chemical properties, biological activity, and clearance rates.[18] Even for PFOA and PFOS, the Office of Water's conclusion that the concentrations of the two substances can be combined has not been subject to appropriate, independent peer review and is not substantiated by the scientific literature.

In addressing the presence of multiple contaminants at a location, EPA's Superfund guidance provides the following advice for modifying the target hazard quotient (THQ) to generate the appropriate screening level –

> The THQ input . . . can be modified from the default of 1. How much it should be modified is a user decision, but it could be based upon the number of contaminants being screened together. For example, if one is screening two contaminants together, then the THQ could be modified to 0.5. If ten contaminants are being screened together, then the THQ could be modified to 0.1.[19]

Notwithstanding the need for appropriate peer review the Office of Water's suggestion that PFOA and PFOS be treated as equally potent in terms of toxicity, the THQ used for developing the screening levels for PFOA and PFOS when found together should be no lower than 0.5.

In addition, consistent with existing practice when developing risk-based screening levels, the screening level at a HQ of 1 should also be presented. For example, EPA Regional Screening Level tables are released in two versions. One at a cancer risk of 1×10^{-6} and a HQ of 0.1, and one at a cancer risk of 1×10^{-6} and a HQ of 1. This allows the public to understand that the lower screening level is not appropriate for screening all sites and that under many conditions screening with a HQ of 1 is applicable.

---

17 EPA. Regional Screening Levels (RSLs) - User's Guide. Office of Land and Emergency Management. Washington, DC (May 2019). https://www.epa.gov/risk/regional-screening-levels-rsls-users-guide (emphasis added)

18 Patlewicz G *et al.* A Chemical Category-Based Prioritization Approach for Selecting 75 Per- and Polyfluoroalkyl Substances (PFAS) for Tiered Toxicity and Toxicokinetic Testing. *Environ Health Perspec* 127(1):1-5 (2019). https://ehp.niehs.nih.gov/doi/10.1289/EHP4555

19 EPA RSLs 2019.

ACC urges EPA to conduct a robust review of the best available science related to PFOA and PFOS and to the application of the OLEM guidance for identifying remediation goals and screening levels before making recommendations on these two substances. Please feel free to contact me at srisotto@americanchemistry.com or at 202-249-6727 if you would like to discuss these issues further.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

Enclosure